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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY HOAG, LLP PATENT GROUP, WORLD TRADE CENTER WEST 155 SEAPORT BLVD BOSTON, MA 02110			LEAVITT, MARIA GOMEZ	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/681,627	<b>Applicant(s)</b> JUNE, CARL H.
	<b>Examiner</b> MARIA LEAVITT	<b>Art Unit</b> 1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### **Status**

1) Responsive to communication(s) filed on 13 March 2008.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### **Disposition of Claims**

4) Claim(s) 1,3,7-15,17-19 and 21-45 is/are pending in the application.

4a) Of the above claim(s) 10-14,18,21 and 23-45 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1,3,7-9,15,17,19 and 22 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### **Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### **Priority under 35 U.S.C. § 119**

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### **Attachment(s)**

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_

5) Notice of Informal Patent Application

6) Other: \_\_\_\_\_

***Detailed Action***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03-13-2008 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. At page 10 of Applicants' remarks filed on 03-13-2008, Applicants direct the examiner's attention to the date recited in error in the previous office action filed on 12-13-2007, at page 6, wherein the action should had stated "in response to Applicants' response filed on 07-18-2007 and 09-27-2007" and not "Applicants' response filed on 10-06-2006". The examiner appreciates the correction.
3. Status of claims. Claims 1, 3, 7-15, 17-19 and 21-45 are currently pending. Claims 1 and 22 have been amended, and 20, 46-47 have been canceled Applicants' amendment filed on 03-13-2008. This application contains claims 10-14, 18, 21 and 23-45 drawn to an invention nonelected with traverse in the reply filed on 10-30-2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01

4. Therefore, claims 1, 3, 7-9, 15, 17, 19 and 22 are currently under examination to which the following grounds of rejection are applicable.

5. *Rejections maintained in response to Applicant arguments or amendments.*

*Claim Rejections - 35 USC § 102(e)*

The present invention is drawn to methods of inhibition of T cell response in a subject in need of comprising contacting the T cell with an agent that inhibits phosphatidylinositol 3-kinase (P13K) and thus production of IL-2 by T cell. Claim 3 further limits the invention to an inhibitor of phosphatidylinositol-3-kinase, e.g., wortmannin. Note that the only active method step in the claims is the step of contacting a T cell with an agent, such as wortmannin. Claim 22 is broadly interpreted as a subject suffering from any inappropriate or abnormal immune response.

Claims 1 and 3 are remain rejected and claim 22 is rejected under 35 U.S.C. 102(e) as being anticipated by Bonjouklian et al., U.S. Patent No. 5,504,103, Date of Publication, April 2 1996 (hereafter referred to as Bonjouklian et al., ).

Bonjouklian et al., teach methods of treating phosphatidylinositol-3-kinase dependent conditions in a mammal contacting the cell with wortmannin or wortmannin analog (col. 1, line 9; col. 14-16, claims 1-20; col. 6, lines 1-9). While Bonjouklian et al., does not explicitly teach contacting T cells or modulation of lymphokine production (e.g., inhibiting production of IL-2), it is inherent in the methods taught by Bonjouklian et al., that the administration of wortmannin or wortmannin analogs to a mammal results in the inhibition of phosphatidylinositol 3-kinase in any and all cells in mammals which express phosphatidylinositol 3-kinase. T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase. This finding is

supported by the applicant disclosure in Figures 3, 4, 7a and 7b that contacting CD28 positive T cells with wortmannin results in inhibition of phosphatidylinositol 3-kinase. Thus, as it is clear that if T cells express phosphatidylinositol 3-kinase, it is inherently in the method of inhibiting phosphatidylinositol 3-kinase in the cells in a mammal *in vivo* as taught by Bonjouklian et al., that phosphatidylinositol 3-kinase is inhibited in T cells present in that mammal. Furthermore, the inhibition of phosphatidylinositol 3-kinase in T cells necessarily and inherently results in a change in cellular activities dependant on phosphatidylinositol 3-kinase, such inhibition of IL-2 by the T-cell. Moreover, Bonjouklian et al., discloses administration to a mammal of a phosphatidylinositol 3-kinase inhibiting compound for treatment of diseases associated with phosphatidylinositol 3-kinase-dependent conditions including diabetes, inflammation, platelet aggregation, vascular diseases (col. 6, lines 7-9), which are diseases clearly associated with inappropriate immune responses. Though Bonjouklian et al., does not explicitly “in a subject in need of “clearly treatment of treating phosphatidylinositol 3-kinase-dependent conditions in a mammal including diabetes, inflammation, platelet aggregation, vascular diseases such as atherosclerosis, restenosis and others (col. 6, lines 7-9) requires previous discovery and diagnosis of the disease before it can be treated in a subject in need of (col. 6, lines 7-9). Indeed Bonjouklian et al., discloses therapeutic treatments wherein the claimed formulations comprising wortmannin or wortmannin analog are administered to a human subject by different routes (col. 6, lines 19-39) at different doses ( col. 6, lines 55-60). In light of such teachings and absent any factual evidence to the contrary, it is clear that “a subject in need thereof” will necessarily be present when treating phosphatidylinositol 3-kinase-dependent conditions in a human subject.

***Response to Applicant Arguments as they apply to rejection of Claims 1 and 3 under 35***

***U.S.C. 35 U.S.C. 102(e)***

At page 8 of Remarks, Applicants argue that “Applicant has discovered that inhibition of phosphatidylinositol 3-kinase (PI3K) in a T cell can inhibit T cell responses, such as lymphokine production and cellular proliferation”. Additionally, Applicants allege that “this was not recognized by Bonjouklian et al., which discloses analogs of wortmannin and is devoid of any teaching of an ability to inhibit a T cell response and, in fact, any exemplification demonstrating activity in any biological assay. While Bonjouklian et al. provide a non-enabling disclosure of a number of potential indications for which the wortmannin analogs may be used (col. 6, li. 1-19), inhibiting T cell activation in a subject in need thereof is not among them”. Such is not persuasive.

As stated in the paragraph above, while Bonjouklian is silent as to the inhibition of T cell activation in a mammal to whom a phosphatidylinositol 3-kinase inhibiting compound such as wortmannin or wortmannin analogs is being administered, Bonjouklian would have inherently obtained an inhibition of T cell activation since they have performed the steps of the claimed method. Moreover, in contrast to Applicants’ arguments, the administration to a mammal of a phosphatidylinositol 3-kinase inhibiting compound for treatment of **widely divergent** diseases associated with phosphatidylinositol 3-kinase-dependent conditions such as diabetes, inflammation, platelet aggregation, vascular diseases (col. 6, lines 7-9), requires previous discovery and diagnosis of the disease. In light of such teachings and absent any factual evidence to the contrary, it is clear that “a subject in need thereof” will necessarily be present when treating phosphatidylinositol 3-kinase-dependent conditions in humans. It is also noted that “a

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subject in need thereof" is a recitation of the intended use or function of the claimed method of contacting the T cell with an agent which inhibits phosphatidylinositol 3-kinase in T cells and fails to impart any physical or structural properties to the said method. Moreover, Bonjouklian teaches preferred embodiments for therapeutic treatment wherein the claimed formulations comprising wortmannin or wortmannin analog are administered to a human subject by different routes (col. 6, lines 19-39) and at different doses ( col. 6, lines 55-60).

At page 8 of remarks, Applicants contend that "upon reviewing the disclosure of Bonjouklian et al., it is apparent that Bonjouklian et al. only recognized the utility of their wortmannin analogs in the treatment of cancer, and not inhibition of T cell activation, as evidenced by the following statements:

"PI 3-kinase appears to be an important enzyme in signal transduction, with particular implications relative to mitogenesis and the malignant transformation of cells" (col 2, li. 14-15, emphasis added)

"[T]he present invention provides a method for treating phosphatidylinositol 3-kinase-dependent conditions, particularly neoplasms" (col 2, li. 34-36, emphasis added)

"[A]n especially preferred embodiment of the present invention includes a method of treating phosphatidylinositol 3-kinase-dependent neoplasms, particularly various lymphosarcomas, with a compound of formula I. Other PI 3-kinase-dependent neoplasms include, for example, adenocarcinoma of the female breast, colon cancer, epidermid cancers of the head and neck, leukemia, melanoma, ovarian carcinoma, plasma cell myeloma, and squamous or small-cell lung cancer."

Moreover, Applicants argue "the only disease that is recited in the claims is "a neoplasm" (claim 13)". Thus Applicants contend "it is very clear that Bonjouklian et al. never envisioned the use of wortmannin analogs for inhibiting a T cell response. In fact, a person of ordinary skill in the art would recognize that the inhibition of a T cell response would be undesirable in the context of treating a neoplastic condition. Bonjouklian et al., therefore, does not teach or suggest

amended claim 1 but, in fact, teaches away from the now claimed method "for inhibiting T cell activation in a subject in need thereof". Such is not persuasive.

At the outset, the examiner disagrees with Applicants' positions that "Bonjouklian et al. only recognized the utility of their wortmannin analogs in the treatment of cancer" [emphasis added]. Preferred embodiments of Bonjouklian et al. include treatment of diseases such as inflammation (e.g., allergies) associated with abnormal enhanced immune response. It is noted that case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. *Bristol-Myers*, 246 F.3d at 1379; see also *In re Donohue*, 766 F.2d at 533.

It is also noted that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

***Claim Rejections - 35 USC § 112 - enablement***

To the extent that claims 1, 15, 17, 19 and 22 broadly embrace an *in vivo* method of treating a human subject suffering from an autoimmune condition comprising inducing unresponsiveness to an antigen in a T cell wherein the antigen is an autoantigen so as to treat an inappropriate immune response against its own tissues, the following rejection applies.

Claims 15, 17, 19 and 22 remain and claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

An *in vitro* method for inhibiting T cell activation as assessed by production of IL-2 comprising stimulating a T cell through the TCR/CD3 complex and CD28 and further contacting said T cell with an agent wherein the agent is selected from the group consisting of Wortmannin, quercetin and LY294002, thereby inhibiting the activity of phosphatidylinositol 3-kinase within the T cell,

does not reasonably provide enablement for claims directed to a method of inducing unresponsiveness to an antigen in a T cell with the intended use of treating a human subject suffering from an autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, when given the broadest possible interpretation, encompass a method for inducing unresponsiveness to an autoantigen in a T cell resulting with the contemplated use of treating a subject suffering from an autoimmune disorder. The subject could be reasonably construed as a human subject suffering from any type of autoimmune disease e.g., rheumatoid arthritis, Crohn's disease, psoriasis, asthma, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy (Specification p. 9, lines 14-21; lines 32-37). The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including treatment of a complex autoimmune disorder have to be examined and considered for patentability regarding the broadly claimed methods.

The instant specification discloses on pages 17, Example 4, the effects of Wortmannin, which inhibits the activity of protein tyrosine kinases in Jurkat cells that were stimulated with CD28 antibody. Moreover, Example 5, at page 18 teaches that Wortmannin inhibits stimulation of T cells as measured by IL-2 production induced by costimulation with B71 or B7-2 in conjunction with CD3 stimulation. The results demonstrate that T cell activation can be inhibited by treatment of the T cells with Wortmannin, which inhibits the activity of protein tyrosine kinases. Further, Applicant contemplates at page 9, lines 37 bridging to page 10, lines 1-10, numerous autoimmune diseases where it is desirable to downmodulate an immune response by inducing T cell unresponsiveness, e.g., arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, allergies, contact dermatitis, psoriasis. However, the as-filed application is silent about any factual data disclosing a method of treating autoimmune diseases in a subject. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcome by the as-filed application. Though, the specification teaches that a phosphatidylinositol 3-kinase inhibitor can inhibit production of IL-2 induced by CD28 ligation and thus induces unresponsiveness to an antigen, the broad aspects of treating an autoimmune disease by administering T cells to a subject is not reasonably enable for the full scope embraced by the claims.

In relation treatment of autoimmune disorders by administration of T cells said cells treated to be unresponsive to an autoantigen as contemplated in the specification at page 9, lines 14-22, post-filing art teaches that the cause of autoimmune disorders is generally considered to

be T cell mediated, however events involved in the treatment of autoimmune diseases are more complicated than merely treating the cell mediated immune response. This complex pathogenesis is reflected in the variable treatments of autoimmune disorders to immunosuppressants. For example, Rott et al., (Clinical Review, 2005, 716-720) teach that patients with rheumatoid arthritis were treated with concomitant immunosuppressant while patients with Crohn's disease did not follow the same regimen of concomitant immunosuppressant (p. 717, col. 2, last paragraph). The different treatments result in distinct immune responses, including immune responses to therapeutic antibodies, development or unmasking of autoimmune disorders and even drug induced lupus after administration of drugs for treatment of autoimmune diseases (e.g., TNF- $\alpha$  inhibitors) (p. 718, col. 2). Other treatments for autoimmune disorders comprise administration of hematopoietic stem cells which give rise to B and T lymphocytes, monocytes, macrophages, and dendritic cells. However, despite a moderate success in the treatment of some autoimmune diseases in animal models by transfer of hematopoietic cells, including treatment of type 1 diabetes, systemic lupus erythematosus and autoimmune encephalomyelitis, Sykes et al., (Nature 2005, pp. 620-627) teaches the unpredictability of using hematopoietic-cell transplantation therapy for treatment of autoimmune diseases in humans stating, "although the prevention of autoimmunity might some day be clinical feasible, at the moment we cannot predict such a disease accurately enough to justify the use of toxic preventive treatment. Unfortunately, animal studies show that preventing the onset of autoimmunity is much easier than reversing established disease" (p. 620, col. 2, paragraph 3) and "to extend observations from these animal models to humans, several factors must be borne in mind: impact of the complex and varied genetics of humans; the effect of different reagents used and different responses to

treatment modalities; the impact of concurrent and complicating co-morbidities in the patients; and the ability to regenerate an immune system after lymphoablative therapy" (p. 621, col. 1 last paragraph bridging to col. 2, paragraph 1). The foregoing observations are especially relevant to the method of inducing unresponsiveness to an antigen in a T cell population and further administering the T cell population to a subject suffering from an autoimmune disease for treatment as envisioned in the instant application, because even assuming the induction of tolerance in autoimmune diseases to an autoantigen at the site of the administration, mobilization of T cells, conditioning regimen, toxicity, outcome, source of T cells, and post administration follow-up need to be disease specific. As the result, claiming broadly a genus of methods for treatment of autoimmune diseases in a subject by T cell wherein unresponsiveness to an autoantigen has been induced, and thus inhibiting production of D-3 phosphoinositides, has not been addressed by the as-filed specification. Hence, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant method to identify an enormous number of treatments of autoimmune diseases in a mammal as broadly or generically contemplated.

*Response to Applicant Arguments as they apply to rejection of Claims 1, 15, 17, 19 and 22  
remain under 35 U.S.C. 112, first paragraph*

With respect to the induction of antigen-specific unresponsiveness, Applicants argue at page 9 of Remarks, that "it is well-recognized that presentation of an antigen in the absence of costimulatory activity, or the presence of agents that inhibit a costimulatory signal, leads to the development of tolerance. This is shown, for example, in Figure 1 of Liu et al., cited by the

Examiner in the instant Office Action. Moreover, the literature is replete with examples of the induction of tolerance by blocking costimulatory activity. One of ordinary skill in the art would, therefore, readily recognize that the agents of the instant methods, which block costimulatory activity by inhibiting PI3K, would antigen-specific unresponsiveness" and as such there is enabling disclosure for the claimed invention. Such is not persuasive.

Although Applicants submit that the scope of the claims is enabling because it encompasses the induction of antigen-specific unresponsiveness which is well-known in the art, the instant claims are broadly interpreted in the context of treating subject suffering from an autoimmune disorder. There is not other disclosed utility for the claimed method. It is noted that claim 20 reciting "the method comprising further administering the T cells to a subject" has been canceled and claim 22 has been amended to change its dependency from now canceled claim 20 to claim 1, apparently in an effort to dissociate the claimed method from a method of treating autoimmune disorders. The instant specification contemplates at page 9, lines 37 bridging to page 10, lines 1-10, numerous autoimmune diseases where it is desirable to downmodulate an immune response by inducing T cell unresponsiveness, e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, contact dermatitis, psoriasis, systemic lupus erythematosus and others. However, the claimed invention is not enabling for treating autoimmune disorders as defined by any of the above diseases. This is because, although the claimed methods are not limited to any particular application requiring any particular treatment of an autoimmune disorder, with regard to claim breadth, the standard under 35 USC § 112, first paragraph, entails the determination of what the claims recite and what the claims means as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the

specification are to be taken into account because the claims are to be given the broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed invention encompasses a method for inducing unresponsiveness to an antigen in a T cell with the contemplated use of treating an autoimmune disorder including rheumatoid arthritis, psoriatic arthritis and others by administration to a subject of a T cell, said unresponsiveness to an antigen in a T cell generated by triggering a primary, antigen-specific signal in a T cell while interfering with an intracellular signal associated with costimulation in the T cell. The Specification at page 3, lines 21-25, recites "As a result of interfering with costimulatory signal transduction, the T cell fails to receive a proper costimulatory signal in the presence of the antigen and antigen-specific unresponsiveness is induced in the T cell". In other words tolerance is induced by blocking the costimulatory activity. As discussed above, and for the reasons of record, the disclosure provided by the applicant is not fully enabled for the scope embraced by the claims because applicant does not provide sufficient guidance to make and use a variety methods for inducing unresponsiveness to an antigen in a T cell with the contemplated use of treating a subject suffering from an autoimmune disease as embraced and set forth by the invention in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art.

*Rejection, Obviousness Type Double Patenting-*

Claims 1, 3, 7-9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 for the reasons of record. Applicants have not addressed properly this rejection.

**New Grounds of objection**

**Specification objection**

*Cross-Referennce to Related Application.* The disclosure is objected to because the cross-reference to related application should appear in first page of the specification and is required to be updated with: is a divisional of U.S. application Serial No. 08/245,282, now U.S. Patent No. 6,632,789, which claims priority to U.S. application Serial No. 08/245,282, filed April 29, 1994, entitled "Methods for Modulating T Cell Responses by Manipulating Intracellular Signal Transduction"; this application is related to PCTAJS95/05213, filed May 1, 1995, entitled 10 "Methods for Modulating T Cell Responses by Manipulating Intracellular Signal Transduction". The entire contents of each of these applications are incorporated herein by reference.

**Conclusion**

Claims 1, 3, 7-9, 15, 17, 19 and 22 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD  
Examiner, Art Unit 1633